REMARKS

Entry of the foregoing and further and favorable consideration of the subject application are respectfully requested in light of the remarks which follow.

Applicants wish to thank the Examiner for the Interview held on August 15, 2002.

I. CLAIM STATUS & AMENDMENTS

As correctly stated in the Office Action Summary, claims 1-26 were pending in this application when last examined. Claims 2-16 stand withdrawn from consideration as being drawn to a non-elected invention. Claims 1 and 17-26 have been examined on the merits, and stand rejected.

By the present amendment, Applicants hereby cancel claims 2-17 without prejudice of or disclaimer as to the subject matter therein. Applicants reserve the right to file a continuation or division application on any canceled subject matter. The present amendment also adds new claim 27. Accordingly, upon entry of the present amendment, claims 1 and 18-27 will be pending in this application.

Claim 1 has been amended to include the subject matter of claim 18. Support for this amendment can be found, at least, in original claims 17 and 18. Claim 19 has been amended to depend on claim 1. Support for new claim 27 can be found in the Specification, at least at page 25, lines 1-15 and page 26, lines 22-29, and in the original claims. Therefore, no prohibited new matter is believed to have been added by these amendments.

The Title of the instant application has been amended to reflect the elected claimed method of treatment as requested by the Examiner. Support for this amendment can be found throughout the Specification and originally filed claims. Therefore, no prohibited new matter is believed to have been added by this amendment.

The Specification at page 1, entitled "CROSSREFERENCE TO RELATED APPLICATIONS" has been amended to reflect the appropriate priority data. No prohibited new matter is believed to have been added by this amendment.

Corrected Figures 1, 2, 10, and 11 are submitted herewith that correct the deficiencies noted in Form PTO-948. Support for these corrected Figures can be found, at least, in the Figures as originally filed. Thus, no prohibited new matter is believed to have been added by these corrected figures.

II. FORMAL MATTERS

a. Title of the Application

The Examiner objected to the Title as allegedly being non-descriptive. See May 24, 2002 Office Action (Paper No. 15), page 2. As noted above, Applicants have amended the Title to reflect the elected claimed method of treatment as requested by the Examiner. Thus, Applicants respectfully request the withdrawal of this objection.

b. Drawings

The Drawings stand objected to as allegedly failing to comply with 37 C.F.R. § 1.84. See May 24, 2002 Office Action (Paper No. 15) page 3 and Form PTO-948. As noted above, corrected Figures 1, 2, 10, and 11 are submitted herewith. These figures correct the deficiencies noted on Form PTO-948 that accompanied the May 24, 2002 Office Action. Applicants respectfully request the withdrawal of this objection.

c. Applicants' Priority Date

The Examiner objected to the Specification and has requested clarification regarding the differences between the first line of the Specification and the priority data contained in the Oath and Declaration. The Examiner also indicated that the filing date of the instant claims is deemed to be the filing date of the priority application PCT/US96/18807, filed November 21, 1996, as the earlier filed priority applications allegedly do not provide written support for the claims directed to "treating rheumatoid arthritis." See May 24, 2002 Office Action page 2 (Paper No. 15).

Applicants have amended the Specification at page 1 to reflect the appropriate priority data. As can be seen from this amendment, as well as the Oath/Declaration, this

application is a national phase entry under 35 U.S.C. § 371 of International Application Number PCT/US96/18807, filed November 21, 1996, and is a continuation-in-part of application serial No. 08/561,521, filed November 21, 1995, now U.S. Patent No. 5,840,299, which is a continuation-in-part of application serial. No. 08/186,269, filed January 25, 1994, now abandoned, and which is a continuation-in-part of PCT/US95/01219, filed January 25, 1994.

It respectfully is submitted that in light of the foregoing amendments and the following discussion, it would be appropriate to accord the instant claims the benefit of, at least, the **November 21, 1995** priority filing date, which is the filing date of application serial No. 08/561,521, now U.S. Patent No. 5,840,299.

The Federal Circuit recently reiterated the legal test for entitlement to priority of a parent case under 35 U.S.C. § 120:

> A claim in a CIP application is entitled to the filing date of the parent application when the claimed invention is described in the parent specification in a manner that satisfies, *inter alia*, the description requirement of 35 U.S.C. § 112. [Citation omitted.]

Therma-Tru Corp. v. Peachtree Doors, Inc., 33 U.S.P.Q.2d 1274, 1276 (Fed. Cir. 1994). For a priority analysis, "[t]he test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'" Ralston Purina Co. v. Far-Mar-Co, Inc., 227 U.S.P.Q. 177, 179 (Fed. Cir. 1985), quoting In re Kaslow, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983). In this analysis, an applicant's prior application "does not have to describe exactly the subject matter [later] claimed. . . . " In re Gosteli, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989), citing In re Lukach, 169 USPQ 795, 796 (C.C.P.A. 1971).

Applicants further note that "[t]he PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." In re Wertheim, 191 U.S.P.Q. 90, 97 (CCPA 1976).

Applicants submit that the claims of the instant application are entitled to, at least, the **November 21, 1995** priority filing date, which is the filing date of application serial No. 08/561,521, now U.S. Patent No. 5,840,299 ("the '299 patent"). The '299 patent teaches a method of treating an inflammatory disease, such as multiple sclerosis ("MS"), by administering a pharmaceutical composition containing the humanized monoclonal ("MAb") 21.6. U.S. Patent No. 5,840,299, claim 27. More specifically, the '299 patent discloses the use of the humanized MAb 21.6 to block α-4 dependent interactions of the VLA-4 receptor. The '299 patent further discloses that the α-4 dependent interaction of the VLA-4 receptor with the VCAM-1 ligand on endothelial cells is an early event in many inflammatory diseases of the central nervous system ("CNS"). More importantly, the '299 patent indicates that the invention is useful for treating undesired diseases and conditions resulting from inflammation of the CNS including MS and **rheumatoid arthritis** ("RA"). U.S. Patent No. 5,840,299, column 14, line 55 to column 15, line 2.

Certainly, the above-noted disclosure provides more than adequate support for the claims of the instant application, which are drawn to a method of using the humanized MAb 21.6 for manufacturing a medicament for treating RA. Thus, the instant claims should be accorded the priority benefit of, at least, the **November 21, 1995** filing date.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claim 17 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. In particular, the Examiner says that a deposit is required with respect to the "21.6" antibody. See May 24, 2002 Office Action, page 4.

Although Applicants have canceled claim 17, Applicants respectfully traverse this rejection for the record. A deposit is not required, because the biological materials are known and available in the public. In this regard, the Examiner is advised that the **mouse** 21/28' CL antibody was known in the art, and its amino acid sequence is described by Dersimonian *et al.*, J. IMMUNOL. 139: 2496-2501 (1987). Specification, page 39, lines 19-22. In addition, all of the sequences, including the amino acid sequence of the human heavy chain variable region (which was used to provide the heavy chain variable

framework sequences) are described in at least Table 5, column 7 and Fig. 7 of the present application. Since the sequence of the mouse 21/28' CL antibody, as well as the human sequences were known and described in the Specification, the description requirement has been met by the Specification. Accordingly, no deposit is required to make the humanized antibody of the claimed invention. See M.P.E.P. § 2404.01. Therefore, Applicants respectfully request the withdrawal of this rejection.

IV. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 17 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite in the recitation of "21.6." See May 24, 2002 Office Action(Paper No. 15), page 5.

Although the claim has been cancelled, Applicants respectfully traverse this rejection for the record. The Specification clearly provides a more than adequate definition of the term "21.6." See for example, Table 5 and Fig. 7 of the present application. Nonetheless, for the sole purpose of expediting prosecution and not to acquiesce to the Examiner's rejection, claim 17 has been canceled without prejudice to or disclaimer thereto. Moreover, claim 1 has been amended to recite the characteristics of the humanized MAb 21.6. Therefore, Applicants respectfully request the withdrawal of this rejection.

V. REJECTION UNDER 35 U.S.C. § 102(e)

Claim 1 stands rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Wayner *et al.*, U.S. Patent No. 5,730,978. See May 24, 2002 Office Action, page 6.

For the sole purpose of expediting prosecution and without acquiescing to the rejection, claim 1 has been amended to recite the particular characteristics of the humanized MAb 21.6. This amendment obviates the rejection.

Wayner fails to anticipate the claimed invention, because Wayner fails to teach or suggest **each** and **every** element of the claimed invention. For example, one structural feature absent from the cited art is the sequence of the mouse 21.6 antibody, which

provides the CDR regions and certain variable region framework residues for the claimed humanized antibodies. Other structural features absent from the cited art are the coordinates of variable region framework positions of the 21.6 antibody specified in the claims for substitution, *i.e.*, at least one position from the group L45, L49, L58, and L69, and at least one position from the group H27, H28, H29, H30, H44, and H71. Thus, Wayner fails to disclose each and every element of the particular characteristics of the humanized MAb 21.6 of amended claim 1.

To anticipate a claim, a single prior art reference must teach, either expressly or inherently, each and every element of the claimed invention. See M.P.E.P. § 2131; Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). Since Wayner fails to teach each and every element of the particular characteristics of the humanized MAb 21.6 of amended claim 1, Wayner cannot be said to anticipate the claimed invention. Therefore, Applicants respectfully request the withdrawal of this rejection.

VI. REJECTIONS UNDER 35 U.S.C. § 103(a)

A. Wayner in view of Bendig '790

Claims 1 and 17-26 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Wayner *et al.* U.S. Patent No. 5,730,978 in view of Bendig *et al.* WO 95/19790 ("Bendig '790"). See May 24, 2002 Office Action, pages 6-7.

Applicants respectfully traverse this rejection for the reasons previously set forth in the Amendment and Reply dated October 17, 2001, and for the reasons set forth below. However, before turning to the rejection, Applicants herein provide a brief background section discussing the etiology and pathology of MS and RA.

1. Multiple Sclerosis

Multiple sclerosis is a chronic demyelinating disease that is characterized pathologically by multiple areas of CNS white matter inflammation, demyelination, and

glial scarring (sclerosis). More specifically, the disease involves inflammatory lesions along the myelin sheath of nerve fibers in the CNS resulting in the demyelination of the myelin sheath. The disease attacks only the CNS, and the peripheral nervous system is not involved. Typically, most myelin sheaths within a lesion are destroyed and the axons are left undamaged.

MS has a **complex** etiology comprising multiple, **unidentified** susceptibility genes and environmental influences. Although numerous theories have been postulated, the cause of MS remains **unknown**. It is believed that the MS is an autoimmune disease, because of its analogy with the disease model of experimental allergic encephalomyelitis (EAE). Both MS and EAE involve immune cells attacking the myelin sheath surrounding nerves in the brain and spinal chord. EAE is induced by immunization with the myelin basic protein. Nonetheless, despite extensive research and the availability of various EAE models in laboratory rodents, the cause MS in humans has not been identified. See Sadiq *et al.*, MERRITT'S TEXTBOOK OF NEUROLOGY, Chapter 128: Demyelinating Diseases, pp. 804-29 (Rowland ed., Williams & Wilkins, Baltimore, 1995) ("Sadiq").

2. **Rheumatoid Arthritis**

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of connective tissue, primarily in the joints. In people with RA, the immune system predominantly targets the cell lining (*i.e.*, synovium) that covers various joints. This inflammation causes erosive bone damage in the affected area. RA is believed to be caused by a yet **unknown** combination of genetic, environmental, hormonal, and reproductive factors. Despite intensive research, the cause of RA remains **obscure**. See El-Gabalawy *et al.*, ARTHRITIS RES. 4(suppl 3):S297-S301 (2002).

3. **Multiple Sclerosis v. Rheumatoid Arthritis**

As discussed, MS and RA are two completely different diseases with divergent etiologies and symptoms. MS affects the myelin sheath of nerve cells in the CNS only which leads to nerve damage, whereas RA affects the cell lining in joints and leads to bone

erosion. Furthermore, the cause of both RA and MS remain unknown. Thus, at the time of the claimed invention one skilled in the art would not reasonably believe that a model of MS would be predictive for RA. In this regard, Applicants submit the following journal articles as evidence that at the time of the claimed invention, EAE and MS were not predictive for RA:

- Bergsteinsdottir *et al.*, JOURNAL OF IMMUNOLOGY, 164(3);1564-1568 (2000) ("Bergsteinsdottir");
- Janis Kuby, IMMUNOLOGY, Chapter 20: Autoimmunity, 477-492 (W.H. Freeman and Co., 1998); and
- Corthay *et al.*, INTERNATIONAL IMMUNOLOGY, 11(&): 1065-1073 (1999) ("Corthay").

Although these references post-date Applicants' priority date, they are evidence of the current state of art, as well as the state of art at the time of the claimed invention.

Bergsteinsdottir attempted to identify a set of common autoimmune disease genes based on experimental models for MS and RA. In particular, Bergsteinsdottir compared the association between different gene regions for subphenotypes of EAE, which is the animal model for MS, to the findings made in the pristane-induced arthritis ("PIA"), which is an animal model for RA. Bergsteinsdottier, page 1564, Abstract. Based on this comparison, Bergsteinsdottir found that while there may be some overlap in the loci of the genes responsible for relapse in EAE and the development of RA, this "does **not** prove that identical genes are involved in the two diseases." Bergsteinsdottir, page 1566, second column, fifth paragraph. In fact, Bergsteinsdottir even indicates that PIA and EAE are induced differently and have different pathogenesis. Bergsteinsdottir, page 1567, second column, second paragraph.

Kuby is significant in that the reference sets forth the animal models for different autoimmune diseases. Kuby, page 491, Table 20-2. Table 20-2 indicates that EAE is the animal model for MS. EAE is **not** indicated as a model to study RA. Instead, autoimmune arthritis ("AA") is the animal model for RA. Kuby, page 491, Table 20-2; page 492, second column, second paragraph. Moreover, EAE is induced by immunization with the

myelin basic protein, whereas, AA is induced by immunization of *M. tuberculosis* proteoglycans. Thus, the autoimmune response involves immune recognition of two divergent molecules affiliated with different diseases and anatomic regions. These disease models clearly involve different mechanisms of action. Accordingly, Kuby highlights the recognition in the art for the need for different animal models for both MS and RA.

Corthay studied the effects of collagen-induced arthritis ("CIA") in the development of αβ T and γδ T cells. CIA is another mouse model for arthritis involving immunization with collagen. Corthay compared the results to the other animal models for autoimmune diseases, especially EAE, the animal model of MS. Corthay found that γδ T cells play a role in EAE (an animal model for MSs), but **not** in CIA (an animal model for arthritis). See Corthay, page 1072, first column, second paragraph. This suggests divergent mechanisms of action for MS and arthritis. Additionally, the method of induction involves two disparate molecules and distinguishable anatomic domains in the animal (i.e., brain v. joint).

4. General Arguments As to the Obviousness Rejection

Applicants believe that a *prima facie* case of obviousness against the claimed invention has not been adduced because the cited references: (1) fail to teach or suggest each and every element of the claimed invention; (2) lack a suggestion to combine/modify the reference teachings to arrive at the claimed invention; (3) do not contain a reasonable expectation of success at arriving at the claimed invention.

To establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art references must teach or suggest each and every element of the claimed invention. See M.P.E.P. § 2143.03; In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); In re Zurko, 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Second, there must be some suggestion or motivation in the references to either modify or combine the reference teachings to arrive at the claimed invention. See M.P.E.P. § 2143; In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). This

element requires that an objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references to arrive at the claimed invention. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In other words, the Examiner must provide a logical reason as disclosed in the prior art at the time of the invention for combining the references along the lines of the invention. Otherwise, the use of such teachings as evidence of non-obviousness will entail impermissible hindsight. Ex parte Stauber, 208 U.S.P.Q. 945, 946 (Bd. App. 1980).

Third, the prior art must provide a reasonable expectation of success. See M.P.E.P. § 2143.02; Vaeck, 947 F.2d at 488, 20 U.S.P.Q.2d at 1438; In re Merck & Co., Inc., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986).

a. Failure to Teach Each & Every Element

As to the first required element for establishing a *prima facie* case of obviousness, Applicants submit that the prior art fails to teach or suggest the treatment of RA, as well as the use of the particular humanized 21.6 antibody to treat RA.

As discussed above, Wayner fails to teach each and every element of the particular characteristics of the humanized MAb 21.6 of the claims. One structural feature absent from the cited art is the sequence of the mouse 21.6 antibody, which provides the CDR regions and certain variable region framework residues for the claimed humanized antibodies. Other structural features absent from the cited art are the coordinates of variable region framework positions of the 21.6 antibody specified in the claims for substitution, *i.e.*, at least one position from the group L45, L49, L58, and L69, and at least one position from the group H27, H28, H29, H30, H44, and H71. There is no explicit or implicit suggestion in the references either alone or in combination which would lead the skilled artisan to this combination of elements in this antibody for use in the claimed method of amended claim 1 or any dependent claim.

Bendig '790 is directed towards treating MS and not RA.

b. Lack of Suggestion to Combine/Modify the Prior Art Teachings

As to the second element of the test for obviousness, Applicants submit that the prior art references fail to provide the requisite suggestion and/or motivation for one of ordinary skill in the art to combine and/or modify the references to arrive at the claimed invention. As discussed above, Wayner fails to teach the treatment of RA, as well as, the particular characteristics of the humanized MAb 21.6 of the claims.

The Examiner relies on Bendig '790 as teaching the use of the particular humanized 21.6 antibody to treat MS. In particular, the Examiner has stated that while Bendig '790 is directed towards treating MS and not RA, it does teach testing in laboratory animals having EAE, which is purportedly a known animal model for arthritis in addition to MS. See May 24, 2002 Office Action, page 7. However, Applicants submit that this conclusory statement is **not** supported by either the cited references or the knowledge known in the art at the time of the claimed invention. In other words, neither Bendig '790 nor Wayner suggest that EAE is a suitable animal model to study RA in addition to MS at the time of the claimed invention.

As discussed above, MS and RA are two completely different diseases with divergent etiologies and symptoms. For instance, MS is a chronic inflammatory and demyelinating autoimmune disease characterized by inflammatory lesions along the myelin sheath of nerve fibers in the CNS. MS is localized in the CNS. MS is thought to be an autoimmune disease, in particular because of its analogy with EAE. EAE is induced by immunization with the myelin basic protein. However, despite extensive research and the availability of various EAE models in laboratory rodents, the etiology of human MS has not been completely elucidated.

In contrast, RA is an autoimmune disease that causes chronic inflammation of a connective tissue, primarily in the joints. In this disease condition, the immune system targets the cell lining in joints, not the cells of the nervous system as in MS. RA is believed to be caused by a yet **unknown** combination of genetic, environmental, hormonal, and reproductive factors. Despite intensive research, the cause of RA remains **obscure**.

Thus, while both diseases were classified as autoimmune diseases at the time of the claimed invention, there was no meaningful similarity between the two to suggest that an animal model for one would be suitable for the other. Moreover, even today, the etiologies and pathologies of both remain unknown. Thus, those skilled in the art at the time of the claimed invention, and even today, would have reasonably believed that the MS and EAE are **different** and **distinguishable** from MS. As such, EAE models and methods of treatment for MS would not have been predictive for RA. To suggest otherwise amounts to proceeding with no reasonable expectation of success.

Thus, contrary to the unsupported assertion made in the rejection, the state of the art at the time of the claimed invention, as evidenced by the above-discussed references, would not consider EAE to be a known model for RA, in addition to MS. Thus, there would be no logical reason at the time of the claimed invention to combine the reference teachings to arrive at the claimed invention. Thus, there is no motivation to use EAE to study RA.

At best, it appears that the rejection employs an "obvious to try" rationale to arrive at the claimed invention. However, it is well established that in moving from the prior art to the claimed invention, one cannot base a determination of obviousness on what one of ordinary skill in the art might try or find obvious to try. In re O'Farrel, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Indeed, the proper test requires determining what the prior art would have led the skilled artisan to do. However, as discussed above, references fail to teach or suggest treating RA.

c. No Reasonable Expectation of Success

As discussed above, those skilled in the art at the state of the art at the time of the claimed invention would have reasonably believed that MS and RA were two completely different diseases with divergent etiologies and symptoms. Furthermore, as illustrated in Kuby and Corthay, the art at the time of the claimed invention recognized the need for different animal models for MS and RA. As a result, there is no logical reason let alone an

expectation of success as disclosed in the prior art at the time of the invention for combining the references to achieve the claimed invention.

Thus, in view of the above, the claimed invention is not obvious over the cited references because the cited art references: (1) fail to teach or suggest each and every element of the claimed invention; (2) lack a suggestion to combine/modify the reference teachings to arrive at the claimed invention; (3) do not contain a reasonable expectation of success at arriving at the claimed invention. Therefore, Applicants respectfully request the withdrawal of this rejection.

B. Wayner in view of Monshizadegan or Yednock, and further in view of Queen, Bendig '683, and Kettleborough

Claims 1 and 17-26 also stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Wayner *et al.* (U.S. Patent No. 5,730,978) in view of Monshizadegan *et al.*, AGENTS ACTIONS 39: C177-179 (1993) or Yednock *et al.* U.S. Patent No. 5,530,101 and further in view of known methods to humanize antibodies as taught by Queen *et al.* U.S. Patent No. 5,530,101, Bendig *et al.* WO 92/15683 ("Bendig '683"), and Kettleberough *et al.*, PROTEIN ENGINEERING 4: 773-783 (1991). See May 24, 2002 Office Action (Paper No. 15), pages 7-8.

Applicants respectfully traverse this rejection for the reasons cited immediately above, and for the reasons set forth below.

The deficiencies of Wayner are discussed above. In particular, Wayner fails to teach or suggest the treatment of RA. Wayner also fails to teach or suggest the particular characteristics of the humanized MAb 21.6 of the claims.

Monishizadegan fails to remedy the deficiencies of Wayner. Monishizadegan is cited as teaching the 21.6 VLA-4 antibody. While Monishizadegan may discuss the 21.6 antibody, the reference fails to provide an enabling disclosure of how to make the antibody or provide the sequence of the 21.6 antibody. The Monishizadegan reference does not reference a deposit or provide the amino acid sequence of the variable domains that would

allow reproduction of the antibody. As the Examiner has noted, exact reproduction of an antibody without deposit or sequence information entails undue experimentation.

Further, attached hereto is the Declaration of Dr. Ted Yednock ("Yednock Declaration"), one of the authors of the reference and a co-inventor of the present application. The Yednock Declaration was submitted with the Amendment and Reply of August 4, 1997 in application serial No. 08/561,521 (now U.S. Patent No. 5,840,299) to rebut an obviousness rejection. This declaration was accepted by the Office. Dr. Yednock's Declaration confirms that the 21.6 antibody of Monishizadegan was not made publicly available to others notwithstanding the discussion of the antibody in the cited reference. Accordingly, Monishizadegan does not provide an enabling disclosure of the mouse 21.6 antibody. Without availability of the mouse 21.6 antibody, one could not know the sequence of its variable regions, and perforce could not have produced humanized 21.6 antibody incorporating CDR regions and the selected variable region framework residues from the mouse 21.6 antibody.

The Yednock patent also fails to cure the deficiencies of the other primary references. Yednock is cited as teaching the use of $\alpha 4\beta 1$-specific antibodies, including the 21.6 antibody, to inhibit $\alpha 4$-dependent interactions of VLA-4 to reduce inflammation. However, Yednock fails to teach the treatment of RA using the specific antibody claimed. The Examiner indicates that while Yednock is directed towards treating MS with the $\alpha 4\beta 1$-specific antibodies, and not RA, it does teach testing in laboratory animals having EAE. Again, the Examiner incorrectly relies on EAE as model for RA. Applicants herein reiterate the arguments made above regarding the EAE model and RA.

Furthermore, as noted by the Examiner (May 24, 2002 Office Action, page 8, lines 5-6) both Monishizadegan and Yednock are silent as to the exact sequences of the 21.6 specific antibodies and the humanized antibodies derived therefrom. As the Examiner has noted, exact reproduction of an antibody without deposit or sequence information entails undue experimentation. Accordingly, without knowledge as to the exact sequences it would take undue experimentation to make the claimed humanized antibody. Thus, Wayner, Monishizadegan, and Yednock fail to teach or suggest the particular

characteristics of the humanized MAb 21.6 let alone a method of using the antibody to treat RA as claimed.

The Examiner relies on the secondary references of Queen, Bendig '683, and Kettleborough as teaching general methods and advantages for humanizing antibodies. However, it well established that the patentability of a composition is determined from the structure of the composition itself and not the existence of a general method for producing such compositions. In this regard, the Federal Circuit has stated the following:

> The question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.
>
> The existence of a general method . . . is **essentially irrelevant** to the question whether the specific molecules themselves would have been obvious.

In re Deuel, 34 U.S.P.Q.2d 1201, 1214 (Fed. Cir. 1995) (emphasis added). Although the cited secondary references may provide general criteria for determining which human variable regions framework residues should be substituted, the actual residues vary for different antibodies, and are determined by molecular modeling of the particular mouse antibody to be humanized. As Deuel makes clear, the patentability of a composition is determined from the structure itself and not from the existence of a general method for producing such compositions. Absent a teaching of the specific amino acid substitutions at the specific positions recited in the claimed antibodies, the existence of general principles for producing humanized antibodies is thus, "essentially irrelevant." Id. Thus, the cited secondary references do not cure the defects of the primary references. Accordingly, the secondary references cannot be combined with any of the primary references in a manner to overcome the defects inherent to all the references to arrive at the claimed invention. Therefore, Applicants respectfully request the withdrawal of this rejection.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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Attachment to Amendment and Reply

Marked-up Copy of Specification

([bracketed] items deleted; underlined items added)

The Title at page 1, lines 4-5.

[THERAPEUTIC USES] THE USE OF HUMANIZED ANTIBODIES AGAINST ALPHA-4 INTEGRIN IN THE TREATMENT OF Rheumatoid ARTHRITIS

Paragraph at page 1, lines 6-10.

CROSSREFERENCE TO RELATED APPLICATIONS

This application is a national phase entry under 35 U.S.C. § 371 of International Application Number PCT/US96/18807, filed November 21, 1996, and is a continuation-in-part of [USSN] application serial No. 08/561,521, filed November 21, 1995, now U.S. Patent No. 5,840,299, which is a continuation-in-part of application serial. No. 08/186,269, filed January 25, 1994, now abandoned, and which is a continuation-in-part of PCT/US95/01219, filed January 25, 1994, now abandoned. [which is] The above-identified applications are hereby incorporated by reference in their entirety for all purposes.

Attachment to Amendment and Reply

Marked-up Copy of Amended Claims 1, 18, and 19

([bracketed] items deleted; underlined items added)

1. (Once Amended) A method of using a humanized antibody to alpha-4 integrin in the manufacture of a medicament for treating [a disease selected from the group consisting of asthma, atherosclerosis, AIDS dementia, diabetes, inflammatory bowel disease,] rheumatoid arthritis [, transplant rejection, graft versus host disease, tumor metastasis, nephritis, atopic dermatitis, psoriasis, myocardial ischemia, and acute leukocyte mediated lung injury] , wherein the humanized antibody is a humanized form of the mouse 21.6 antibody, wherein said humanized antibody comprises a humanized heavy chain and a humanized light chain:

(1) the humanized light chain comprising three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 21-6 immunoglobulin light chain variable domain designated SEQ ID No:2, and a variable region framework from a human kappa light chain variable region framework sequence except in at least one position selected from a first group consisting of L45, L49, L58 and L69, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin light chain variable region framework; and

(2) the humanized heavy chain comprising three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 21-6 immunoglobulin heavy chain variable domain designated SEQ ID No:4, and a variable region framework from a human heavy chain variable region framework sequence except in at least one position selected from a second group consisting of H27, H28, H29, H30, H44, H71, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin heavy chain variable region framework;

Attachment to Amendment and Reply

Marked-up Copy of Amended Claims 1, 18, and 19

([bracketed] items deleted; underlined items added)

wherein the humanized immunoglobulin specifically binds to alpha-4 integrin with a binding affinity having a lower limit of about 10^7 M^{-1} and an upper limit of about five-times the binding affinity of the mouse 21-6 immunoglobulin.

18. (Once Amended) The method according to claim [17] 1, wherein the humanized antibody [comprises a humanized heavy chain and a humanized light chain:

(1) the humanized light chain comprising three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 21-6 immunoglobulin light chain variable domain designated SEQ ID No:2, and a variable region framework from a human kappa light chain variable region framework sequence except in at least one position selected from a first group consisting of L45, L49, L58 and L69, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin light chain variable region framework; and

(2) the humanized heavy chain comprising three complementarity determining regions (CDR1, CDR2 and CDR3) having amino acid sequences from the corresponding complementarity determining regions of the mouse 21-6 immunoglobulin heavy chain variable domain designated SEQ ID No:4, and a variable region framework from a human heavy chain variable region framework sequence except in at least one position selected from a second group consisting of H27, H28, H29, H30, H44, H71, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21-6 immunoglobulin heavy chain variable region framework;

wherein the humanized immunoglobulin] specifically binds to alpha-4 integrin with a binding affinity having a lower limit of about 10^7 M^{-1} and an upper limit of about five-times the binding affinity of the mouse 21-6 immunoglobulin.

Attachment to Amendment and Reply

Marked-up Copy of Amended Claims 1, 18, and 19

([bracketed] items deleted; underlined items added)

19. (Once Amended) The method according to claim [18] 1, wherein the humanized light chain variable region framework is from an RE1 variable region framework sequence except in at least one position selected from the first group, and except in at least one position selected from a third group consisting of positions L104, L105 and L107, wherein the amino acid position is occupied by the same amino acid present in the equivalent position of a kappa light chain from a human immunoglobulin other than REl.

Attachment to Amendment and Reply

Declaration of Ted Yednock